BMJ

BMJ 2012;345:e4944 doi: 10.1136/bmj.e4944 (Published 7 August 2012)

RESEARCH

Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis

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Abstract

Objectives To evaluate the risk of venous thromboembolic events associated with the use of progestin-only contraception and whether that risk differs with the mode of drug delivery (oral, intrauterine, or depot injection).

Design Systematic review and meta-analysis of randomised controlled trials and observational studies.

Data sources Pubmed, Embase, Cochrane Library, and reference lists of relevant reviews.

Study selection Randomised controlled trials and case-control, cohort, and cross sectional studies with venous thromboembolic outcome for progestin-only contraception reported relative to a non-hormone comparator group.

Data extraction Data were extracted by two independent investigators, and consensus for inclusion was reached after assessment by additional investigators.

Results Among the 2022 unique references identified by all searches, eight observational studies fulfilled inclusion criteria. A total of 147 women across all studies were diagnosed with a venous thromboembolic event while taking progestin-only contraception, and the summary measure for the adjusted relative risk of a venous thromboembolic episode for users versus non-users of a progestin-only contraceptive was, based on the random effects model, 1.03 (95% CI 0.76 to 1.39). Subgroup analysis confirmed there was no association between venous thromboembolic risk and progestin-only pills (relative risk 0.90 (0.57 to 1.45)) or a progestin intrauterine device (0.61 (0.24 to 1.53)). The relative risk of a venous thromboembolic event for users of an injectable progestin versus non-users was 2.67 (1.29 to 5.53).

Conclusions Published data assessing the risk of venous thromboembolism in women prescribed progestin-only contraception are limited. In this meta-analysis of eight observational studies, the use of progestin-only contraception was not associated with an increased risk of venous thromboembolism compared with non-users of hormonal contraception. The potential association between injectable progestins and thrombosis requires further study.

Introduction

Since their introduction in the 1960s, combined oestrogen-progestin oral contraceptives have been associated with an increased risk of venous thromboembolic events. This thrombotic risk was attributed to the oestrogen content, which prompted the development of oral contraceptives containing less oestrogen. Use of formulations containing lower dose oestrogen still confer about twofold to fourfold increased risk of venous thromboembolic events compared with non-use.[1-5] Epidemiological data suggest that subsequent changes in the composition of combined oral contraceptives by altering the progestin content can exacerbate thrombotic risk. Accordingly, newer progestins such as desogestrel, gestodene, and norgestimate have been associated with a greater venous thromboembolic risk than the older progestins such as levonorgestrel, lynestrenol, and norethisterone.[4-8] When combined with an oestrogen, the newer progestins increase activated protein C resistance more than older progestins, which may account for the observed increased incidence of venous thromboembolism.[9-12] Despite evidence that progestins may influence the risk of venous thromboembolism, there are only limited data evaluating the association between progestin-only

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Appendix: Search strings used in literature search (as supplied by the author) (see http://www.bmj.com/content/345/bmj.e4944?tab=related#webextra)

contraception and thrombosis. Progestin-only contraception is generally thought to pose little risk of thrombosis and is recommended for women at high risk—such as post partum or with hereditary thrombophilia or a history of venous thromboembolism.[13 14] We performed a meta-analysis to evaluate the risk of venous thromboembolism associated with progestin-only contraception.

Methods

We performed a systematic review and meta-analysis of studies to evaluate the hypothesis that progestin-only contraceptives do not increase the risk of venous thromboembolic events. We conducted a literature search of journal articles published on or before 31 December 2011 using PubMed, Embase, and the Cochrane Database of Systematic Reviews. The index (MeSH or Emtree) fields were queried for the key words "progestin," "progesterone," "progestogen," "progestagen," "gestagen," "contraceptive," "thrombosis," "thromboembolism," and "thrombotic" (see appendix on bmj.com). Because of available resources, we considered only English language publications. We also performed a hand search of all the references included in a previous meta-analysis that analysed progesterone-only contraception and the risk of venous thromboembolic events[15] and a review of contraception in thrombophilic adolescents.[16]

Inclusion criteria

Studies were included if they met all of the following conditions: a randomised trial or case-control, cohort, or cross sectional study (prospective or retrospective); presence of a treatment arm featuring use of progestin-only contraceptives and a control arm with no hormone use; use of progestin for the purpose of contraception only (excluding postcoital contraception); independent analysis of premenopausal women; incidence of venous thromboembolic events (defined as deep venous thrombosis or pulmonary embolism) reported; study featured human data only; one or more of three possible administration routes (oral, injectable, or intrauterine) were considered.

Data extraction

The initial search of the three databases was performed by SM; the references obtained were screened independently by two reviewers (RK and VR). Abstracts were assessed for relevance, and the full text of potentially suitable articles were retrieved. Each of those papers was assessed independently by the two reviewers (RK and VR) for inclusion in the meta-analysis; the reason for exclusion was noted for rejected articles. Two other reviewers (SM and JIZ) read the final subset of papers retained; mutual consensus was required for a study to be included in the analysis.

Validity assessment

Two reviewers (SM and JIZ) independently qualitatively evaluated the risk of confounding and the design quality of selected studies. Observational studies were assessed as suggested by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group.[17] The characteristics of individuals in the case and control groups or exposed and unexposed patients were compared; the use of matching or stratification was noted, and covariates used for adjustment in multivariate analysis were recorded. For randomised trials, the plan was to use the Cochrane Collaboration's tool for assessing risk of bias.[18]

Statistical analysis

We estimated the risk ratio of venous thromboembolism for users of progestin-only oral contraceptives versus non-users. Venous thromboembolism was defined as including both deep venous thrombosis and pulmonary embolism. We assumed that venous thromboembolic events had a low incidence (<10% a year) in women aged <50 years taking oral contraceptives; this was based on previous reports estimating the yearly incidence of those events to about 0.06% per year.[4] For infrequent events, the risk ratio, odds ratio, and rate ratio are considered equivalent measures of relative risk.[19] With this in mind, we used the Comprehensive Meta-Analysis (CMA) version 2.2 software platform, entering each measure of relative risk in the same data table as if it were a risk ratio. The DerSimonian and Laird random effects model was used with the study as the unit of analysis. The primary analysis was performed with the adjusted measures of effect.

As a secondary analysis, we estimated the adjusted risk ratio of venous thromboembolism for users versus non-users of a hormone in each subgroup according to route of administration (oral, injectable and intrauterine). Additionally, an unadjusted odds ratio of venous thromboembolic event for users versus non-users of progestin was calculated using the raw event data. Heterogeneity across studies was estimated by means of the I^2 statistic, itself calculated from the Q statistic. Sensitivity analysis was performed by repeating the primary analysis while excluding selected subgroups in order to determine if they had an inordinate effect on the estimated measure of effect.

Results

A total of 2045 references were identified: 1827 from PubMed, 215 from Embase, and none from the Cochrane Database of Systematic Reviews (fig 1⇓). Two journal articles were identified from reading reviews of the subject matter,[15 16 20 21] and one from personal knowledge of an author.[22] After removal of duplicates, 2022 records remained and were screened for inclusion in the analysis. Of these, 1922 were excluded after review of the abstract for lack of pertinence, leaving 100 articles to be retrieved. The full text of these papers were evaluated: 92 were excluded, with eight remaining for analysis.[20 22-28] The reasons for exclusion were not being a case-control or cohort study or randomised trial (n=41), results not reported separately for a progestin-only arm (n=39), absence of a no hormone arm (n=4), progestin not administered for contraception only (n=4), results for venous thromboembolism not reported (n=3), and old version of a study with a recent update (n=1).

Characteristics of included studies

The methods used by the authors of the eight selected studies are summarised in table 1⇓. Our search found no randomised trial including a group of women taking a progestin-only contraceptive versus a group taking no hormone; three studies were retrospective cohort analyses, and five were case-control studies. All the case-control studies matched participants by age, and all but one study evaluated patients taking a progesterone-only pill with some also including individuals with a depot or intrauterine progestin-only contraceptive. Only two studies made use of stratification, but all of them performed multivariate analysis. The regression techniques varied widely: logistic regression was the most common approach,[20 26-28] followed by Poisson regression[23 24] and Cox modelling.[22 23] Body mass index was the variable most commonly adjusted for, with five sets of authors using it in their model. Two of the three retrospective cohort studies adjusted results for age in

multivariate analysis. After considering these details, our reviewers determined that all of the eight papers retrieved in the search were of sufficient quality to be included in the meta-analysis.

A total of 147 women sustained a venous thromboembolic event, and table 2⇓ shows the results of the articles retained for final analysis. The largest study was that of Lidegaard et al,[24] with 1882 episodes of venous thromboembolism recorded in the combined group of individuals exposed to a progestin or to no hormone, followed by the WHO study,[27] which featured 667 cases of venous thromboembolism for progestin-only users and non-users. The remaining six papers included a total of 777 events. The mean ages of case and control groups or exposed and unexposed groups were similar in the articles where the data were available. Since logistic regression was used in most papers, the odds ratio was the most common measure of effect.

Risk of venous thromboembolism

The adjusted relative risk of a venous thromboembolic event for users of progestin-only contraception versus non-users varied from 0.68 to 1.93, as shown in table 3⇓. None of the studies reported a statistically significant difference in the risk of venous thromboembolic event for users versus non-users of progestin-only contraceptive, whether for subgroups of users or all users versus non-users. However, Lidegaard et al reported the results for three different progestin-only formulations separately.[24] We combined these three risk ratio estimates, corresponding to the three progestins, using the random effect models and setting the study as the unit of analysis. We assumed the three estimates were independent because there was insufficient information to account for their dependence. Hence the confidence interval of the estimate (0.61 to 0.98) may be too narrow (table 2⇓).

The summary measure for the adjusted relative risk of a venous thromboembolic event for users versus non-users of a progestin-only contraceptive was 1.03 (95% CI 0.76 to1.39) with the random effects model (fig 2⇓). This value was similar to the one obtained by combining the crude results (relative risk 1.21 (0.92 to 1.59)). However, the largest study (by Lidegaard et al[24]) could not be included in this latter estimate because the numbers of exposed and unexposed individuals were not provided (fig 3⇓).

Subset analysis was performed on the adjusted results with the random effects model. A total of 54 women developed a venous thromboembolic event while taking a progestin-only pill (excluding the study by Vasilakis et al,[25] which did not specify the route of administration), and they showed no significant increase in risk of venous thromboembolism compared with non-users (relative risk 0.90 (0.57 to 1.45)). On the other hand, the relative risk of an event for users of an injectable progestin formulation versus non-users was 2.67((1.29 to 5.53) (fig 4⇓). Only two studies could be used to compute this value because no other article reported the results separately for that subgroup. Those two papers featured a total of 31 venous thromboembolic events in users of injectable progestins, which represents 21% of all cases in progestin-only users among all of the eight studies. Similarly, only two papers reported the results for the risk of venous thromboembolism in users of a progestin-only intrauterine device, and the combined measure of effect was 0.61 (0.24 to 1.53). These two studies reported 58 thromboembolic events in users of a progestin-only intrauterine device, which corresponds to 39% of all such episodes in progestin-only users among all of the eight studies. Notably, most of the information on these thromboembolic events comes from Lidegaard et al,[24] with 55 venous thromboembolic event episodes in comparison with only three episodes in the paper from van Hylckama Vlieg et al.[26]

Heterogeneity was low, with an I^2 of 24% and P=0.24 for the adjusted results (fig 2⇓). Sensitivity analysis was done by repeating the meta-analysis with one of the studies removed on an iterative basis: for all iterations, the 95% confidence intervals overlapped largely with those of the main analysis (data not shown).

Discussion

The primary objective of this meta-analysis is to assess the risk of venous thromboembolic events in women taking progestin-only contraception compared with non-users. A total of eight studies were included in this analysis, and the summary statistic did not identify a significant risk of venous thromboembolism associated with use of progestin-only contraception. There was a low degree of heterogeneity between studies, and we performed subgroup analysis to determine whether the apparent lack of association with venous thromboembolism was independent of route of administration of progestin (oral, depot injection, or intrauterine device).

All studies except that of van Hylckama Vlieg et al[26] included patients taking an oral progestin; pooling of the results for the five papers reporting results separately for that subgroup indicated no increase in risk of venous thromboembolism for users versus non-users. The oral formulations included in this meta-analysis consisted of numerous different compounds, so it is not possible to evaluate a relation between risk of venous thromboembolism and individual types of progestin. In the studies that included women using a progestin-only intrauterine device, no excess risk of venous thromboembolism was detected. However, our analysis suggests that depot administration more than doubles the risk of venous thromboembolism. Only two studies reported results separately for this subgroup, representing about a fifth of the total number of venous thromboembolic episodes in the progestin-only users for the eight studies.

The relative safety of progestin-only contraception by oral and intrauterine delivery may in part be explained by dose, absorption, or metabolism. The amount of progestin included in a progestin-only "mini-pill" is considerably less than that commonly supplied in a combined oestrogen-progestin oral contraceptive. For instance, norethindrone is the only marketed progestin-only pill marketed in the United States, and when used alone the dose is 0.35 mg daily or about a third of the dose commonly found in combined oestrogen-progestin formulations.[29] Similarly, the levonorgestrel-containing intrauterine device releases about 20 μg of levonorgestrel daily, most of which is concentrated in the endometrium with plasma concentrations ranging between 74 and 166 pg/mL.[30] By comparison, after intramuscular injection of medroxyprogesterone 150 mg, the peak plasma concentration is 2500–7000 pg/mL and remains greater than 430 pg/mL at three months.[31 32]

Different progestins are also known to influence the risk of thrombosis differently. Evidence suggests that third generation progestins such as desogestrel in combination with oestrogen are more prothrombotic than earlier formulations such as levonorgestrel or norethisterone.[4-8 24] Progestins can modulate oestrogen induced activated protein C resistance[12] and have been shown to influence the cellular expression of tissue factor[33 34] as well as circulating tissue factor pathway inhibitor.[10 35] In a mouse model of vascular injury administration of medroxyprogesterone significantly shortened the time to

development of an occlusive thrombus.[36] In the studies included in this meta-analysis, the vast majority of women used older progestins, potentially masking an association with venous thromboembolism. However, the study by Lidegaard et al analysed more than 29 000 women years for a third generation progestin-only pill and failed to show any increased risk associated with its use (adjusted venous thromboembolic event rate 0.64 (95% confidence interval 0.29 to 1.42)).[24]

Strengths and limitations of the meta-analysis

A potential limitation of this study remains the paucity of published literature on the topic, with a total of only eight studies available for analysis and no randomised trials. The inclusion of several recently published large epidemiological studies permits a more robust summary analysis with tighter confidence intervals than a previously published meta-analysis, which evaluated only four studies (without an analysis according to method of delivery).[15] The consistency of the results for different oral formulations reassures the validity of the measure of effect for this group. The subgroup analysis for intrauterine devices and depot injections should be interpreted with caution because of the limited number of studies available for analysis.

Control for confounding in the individual studies was usually limited. Also, selection bias cannot be excluded as the basis of the significant association between depot administration and venous thromboembolism. However, this is unlikely as the study that contributed most to the summary statistic for depot injection specifically excluded highest risk women (that is, those with a personal history of venous thromboembolism).[26] We did not observe evidence of publication or reporting bias. However, the small number of studies limits our ability to formally assess these potential biases.[37] Bias and lack of adjustment for confounders at the level of the individual studies cannot be corrected in the meta-analysis, so the validity of these results is dependent on quality of the primary observational data.

Implications for patient care

Deciding on the optimal contraceptive method is often difficult for women considered at increased risk of venous thromboembolism, such as those with a history of thrombophilia. The World Health Organization and US Centers for Disease Control and Prevention publish similarly titled guidelines on the topic, "Medical eligibility criteria for contraceptive use." All modes of progestin-only contraception are advocated, even for higher risk women such as those with hereditary thrombophilia, history of oestrogen induced venous thromboembolism, or history of recurrent venous thromboembolism.[13 14] This meta-analysis offers further reassurance that such guidance is appropriate. However, only two of the studies were specifically conducted in high risk populations, with a total of 360 women.[22 23] Our analysis also suggests that the relative safety of progestin-only agents may be limited to oral and intrauterine formulations, whereas the thrombotic risk associated with injectable progestin seems to be of similar magnitude to oral contraceptives containing oestrogen.

Conclusion

Collectively, progestin-only contraceptives were not associated with an increased risk of venous thromboembolism compared with non-users in a limited number of observational studies. In the subset of women in this analysis prescribed injectable progestins, there was an approximate twofold increase in thrombotic risk. These results require confirmation as selection bias cannot be excluded. In the interim, we suggest consideration of non-injectable forms of progestin-only contraception for highest risk women.

Contributors: RK and VR performed initial literature searches and data extraction. JIZ and SM performed data extraction, statistical analysis, and coauthored the manuscript. NT provided statistical analysis and editing. KAB performed manuscript review and editing.

Funding: This study was funded by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (grant No UL1 RR025752). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support from US National Institute of Health for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing: No additional data available.

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What is already known on this topic

The risk of venous thromboembolic events associated with use of hormone contraceptives is influenced by the dose of oestrogen and formulation of progestin

Progestin-only contraception is the preferred hormone contraceptive in women considered higher risk for development of venous thromboembolism

What this study adds

This meta-analysis of eight observational studies did not identify an association between oral progestin-only contraception and risk of venous thromboembolism

Subgroup analysis suggests that injectable progestin contraception is associated with an approximate twofold increased risk of risk of venous thromboembolism relative to women not taking hormonal contraception

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Accepted: 28 June 2012

Cite this as: *BMJ* 2012;345:e4944

Tables

Table 1| Characteristics of studies included in review of risk of venous thromboembolic events in women taking progestin-only contraceptives

Study	Inclusion criteria	Baseline risk*	Format	Matching	Stratification†	Adjustment factors in multivariate analysis
Barsoum et al, 2010[28]	Cases: diagnosis of deep vein thrombosis or pulmonary embolism	Average	Case-control	Age and medical record number	No	BMI, recent hospitalisation, recent surgery, nursing home confinement, trauma or fracture, active cancer, leg paresis, varicose veins
Conard et al, 2004[23]	Personal history of VTE with presence of thrombophilia or family history of VTE	High	Retrospective cohort	No	No	BMI, age, thrombophilia
Heinemann et al, 1999[20]	Cases: diagnosis of myocardial, thromboembolic cerebrovascular accident or VTE	Average	Case control	Age	No	BMI, hypertension, smoking, diabetes, alcohol consumption, education
Lidegaard et al, 2011[24]	All Danish women aged 15-49 years in 1995-2009	Average	Retrospective cohort	No	Certainty of diagnosis	Age, calendar year, level of education
Vaillant-Roussel et al, 2011[22]	One episode of VTE during use of combined oral contraceptive or <1 month after stopping	High	Retrospective cohort	No	No	Duration of exposure
Vasilakis et al, 1999[25]	Cases and controls: to have received ≥1 prescription for a progestin alone. Cases: idiopathic VTE	Average	Case-control	Age and general practice	No	BMI, smoking
Van Hylckama Vlieg et al, 2010[26]	Cases: first episode of VTE	Average	Case-control	Age	No	Age
WHO, 1998[27]	Cases: VTE, stroke, or acute myocardial infarction	Average	Case-control	Age	Europe *v* developing countries, history of hypertension, smoking status	BMI, number of live births, hypertension, rheumatic heart disease, family history of premature heart attack

VTE=venous thromboembolic event. BMI=body mass index.

*Subjective assessment based on inclusion criteria.

†Within the group of cancer-free women receiving a progestin-only agent.

Table 2| Progestin exposure characteristics in studies of venous thromboembolic events in women taking progestin-only contraceptives

	No of patients		Progestin used			Duration of exposure	
Study	With a VTE*	Without VTE*	Route	Drug	Dose	Cases or exposed*	Controls or unexposed*
Barsoum et al, 2010[28]	1	1	Oral	Medroxyprogesterone acetate†	5 or 10 mg/day	N/A	
	2	1	Inject	Medroxyprogesterone acetate†	150 or 400 mg		
Conard et al, 2004[23]	3	99	Oral	Chlormadinone acetate	10 mg daily, 18-20 days/cycle	Mean 31.2 (SD 19.7) months	Mean 35.0 (SD 17.7) months
Heinemann et al, 1999[20]	7	54	Oral	N/A		N/A	
Lidegaard et al, 2011[24]	9	N/A	Oral	Norethisterone	N/A	44168 women years	
	6			Desogestrel		29187 women years	
	55		IUD	Levonorgestrel		155149 women years	
Vaillant-Roussel et al, 2011[22]	7	27	Oral	N/A		Median 74 (range 3-434) months	
Vasilakis et al, 1999[25]	2	26	Oral	N/A		N/A	
			Inject				
Van Hylckama Vlieg et al, 2010[26]	20	15	Inject	Medroxyprogesterone	N/A	N/A	
	3	26	IUD	Levonorgestrel			
WHO, 1998[27]	21	63	Oral	Levonorgestrel	0.03 mg	N/A	
				Norgestrel	0.075 mg		
				Ethynodiol diacetate	0.5 mg		
				Lynestrenol	0.5 mg		
				Norethisterone	0.35 mg		
	11	34	IUD	Medroxyprogesterone	150 mg		
				Norethisterone oenanthate	200 mg		

VTE=venous thromboembolic event. N/A=data not available from the journal article. IUD=intrauterine device.

*Single value for combined group provided when breakdown not available.

†Women aged ≤45 years received a progestin for contraception and other indications.

Table 3| Total number of venous thromboembolic events and adjusted relative risk in women taking progestin-only contraceptives or no hormone among included studies

Study	Mean (SD) age (years)		No of patients				Measure of effect used	Adjusted relative risk of VTE for users *v* non-users (95% CI)
			Progestin		No hormone			
	Cases (or exposed)	Controls (or unexposed)	VTE	No VTE	VTE	No VTE		
Barsoum et al, 2010[28]	N/A	N/A	3	2	98	133	Odds ratio	1.20 (0.40 to 3.63)
Conard et al, 2004[23]	29.6 (8.6)	29.7 (8.7)	3	99	6	96	Rate ratio*	0.80 (0.2 to 3.9)
Heinemann et al, 1999[20]	34.5 (6.6)	34.0 (7.4)	7	54	174	1346	Odds ratio	0.68 (0.28 to 1.66)
Lidegaard et al, 2011[24]	N/A	N/A	70	N/A†	1812	N/A‡	Rate ratio§	0.77 (0.61 to 0.98)¶
Vaillant-Roussel et al, 2011[22]	N/A	N/A	7	27	20	102	Rate ratio**	1.30 (0.50 to 3.00)
Vasilakis et al, 1999[25]	N/A	N/A	2	26	13	161	N/A	1.30 (0.3 to 6.8)
Van Hylckama Vlieg et al, 2010[26]	39.9 (N/A)	39.5 (N/A)	23	41	421	1102	Odds ratio	1.38 (0.65 to 2.90)¶
WHO, 1998[27]	31.8 (7.1) for oral, 31.0 (6.2) for injectable	35.4 (6.8)	32	97	635	2288	Odds ratio	1.93 (0.97 to 3.84)¶

VTE=venous thromboembolic event. N/A=information not reported in original paper.

*Obtained from Poisson regression (incidence rate ratio) and Cox proportional hazards regression (hazard ratio); result from the Cox model shown

†Incidence rate/10000 woman years of VTE=2.0 to 3.5, depending on the type of progestin.

‡Incidence rate/10000 woman years of VTE=3.7 for non-users.

§Obtained from Poisson regression (incidence rate ratio).

¶Summary measure for all progestin-only contraceptive users versus non-users calculated based on the results from the different subgroups as reported in the original paper.

**Hazard ratio obtained from Cox proportional hazards regression.

Figures

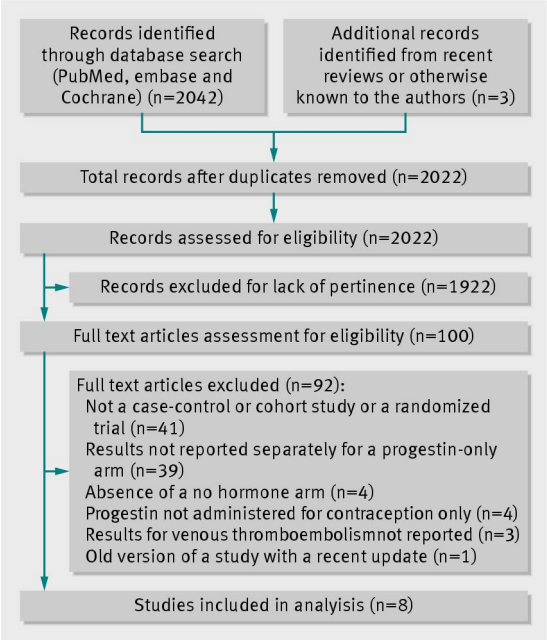
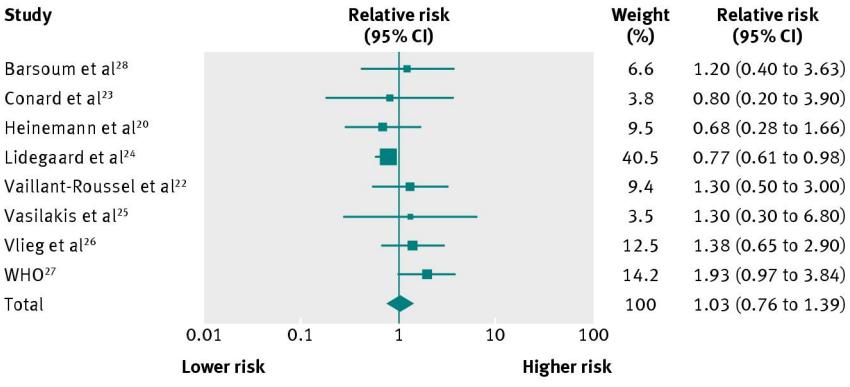
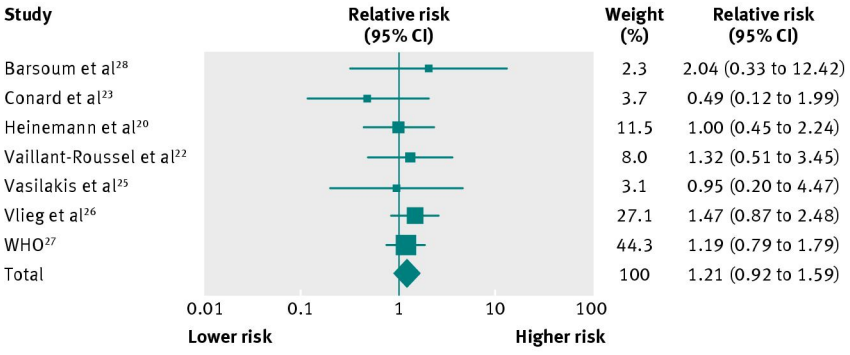


Fig 1 Flow diagram of studies included in meta-analysis



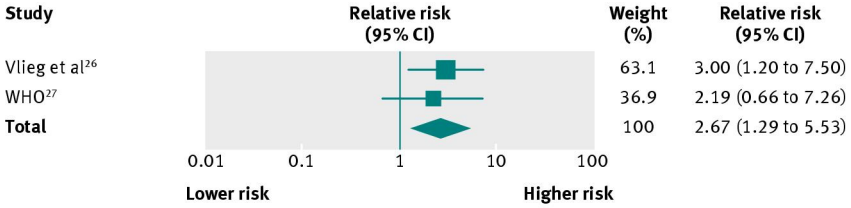
Test for heterogeneity: Q=9.21, df=7, I^2=24%, P=0.24

Fig 2 Adjusted relative risk of venous thromboembolism for users versus non-users of a progestin-only contraceptive, all subgroups combined



Test for heterogeneity: Q=2.79, df=6, I^2=0%, P=0.83

Fig 3 Unadjusted relative risk of venous thromboembolism for users versus non-users of a progestin-only contraceptive, all subgroups combined



Test for heterogeneity: Q=0.17, df=1, I^2=0%, P=0.68

Fig 4 Adjusted relative risk of venous thromboembolism for users versus non-users of a progestin-only contraceptive, injectable formulation only